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Expedient synthesis of a highly substituted tropolone via a 3-oxidopyrylium [5+2] cycloaddition reaction

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Abstract—An expedient ten-step synthesis of a substituted tropolone is described. The synthesis involves a 3-oxidopyrylium [5+2] cycloaddition reaction with acrylonitrile as the key step, affording a highly functionalized [3.2.1]-bicycle **10** as a single regioisomer. The nitrile substituent of the reduced cycloadduct **12** permits efficient ether-bridge cleavage and tropolone **15** is obtained after a final bis-oxidation procedure. The pyranulose acetate cycloaddition precursor was derived from 3-methyl-2-furoate.

Since their discovery, tropolone natural products and synthetic tropolone derivatives have attracted considerable interest due to the unique structure and properties of the tropolone ring (Fig. 1).[1] Numerous tropolone natural products and several synthetic tropolone compounds have shown a range of potent biological activities.[2] Tropolones are also being actively studied in the field of liquid crystal research.[3]

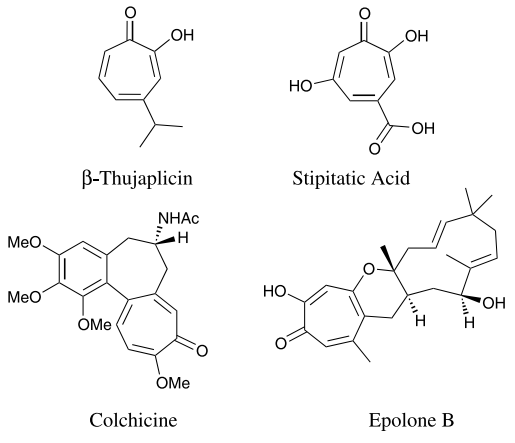
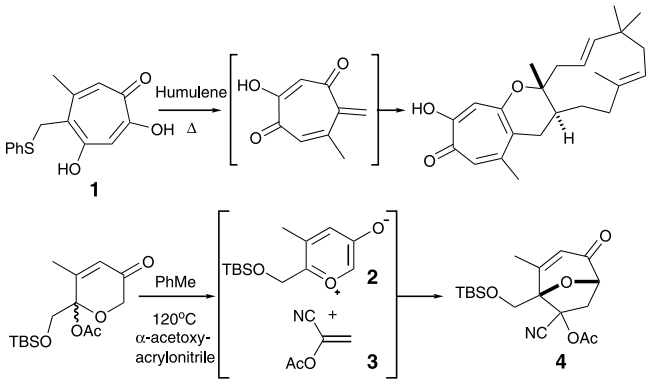


Figure 1.

Despite featuring only seven ring carbon atoms and no stereocentres, the synthesis of substituted tropolones continues to be a considerable synthetic challenge. A recent renewed interest in the ability of colchicine to inhibit tubulin polymerisation has been complemented by elegant new approaches to tropolone structures.[4] We recently disclosed a biomimetic cycloaddition approach to novel tropolone natural products via a tropolone quinone methide derived from a substituted tropolone derivative **1** (Scheme 1).[5,6]



Scheme 1.

Tropolone **1** was derived from cycloadduct **4** which in turn was obtained via a 1,3-dipolar cycloaddition reaction of 3-oxidopyrylium species **2** with ketene equivalent **3**. This [5+2] cycloaddition is a well precedented strategy for the rapid access of functionalized seven-membered ring structures, however until our recent disclosure it had not been applied to tropolone synthe-

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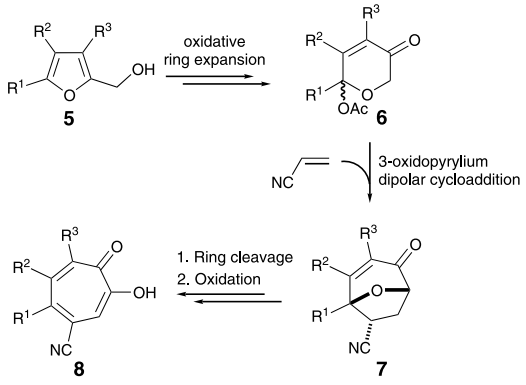
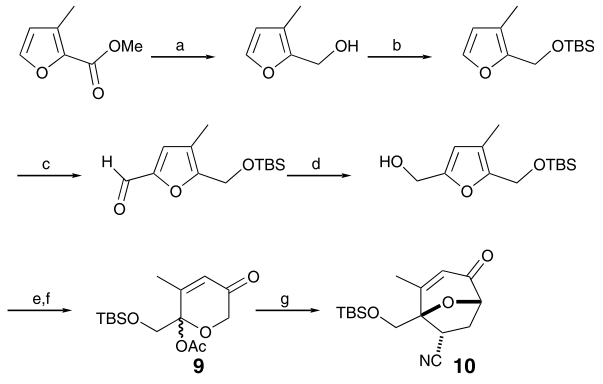
sis.[7] We envisaged that by using this strategy, other substituted tropolones, such as nitrile tropolone **8**, could be accessed (Scheme 2). A suitably substituted furan methanol derivate **5** could be converted into the pyranulose acetate **6** via an oxidative ring expansion (Scheme 2). Thermolysis of **6** in the presence of an acrylonitrile would afford the cycloadduct **7**, which could be transformed into tropolone **8** via ether-bridge cleavage and subsequent oxidation. We herein report the first example of a rapid synthesis of a novel substituted cyanotropolone using this cycloaddition approach.



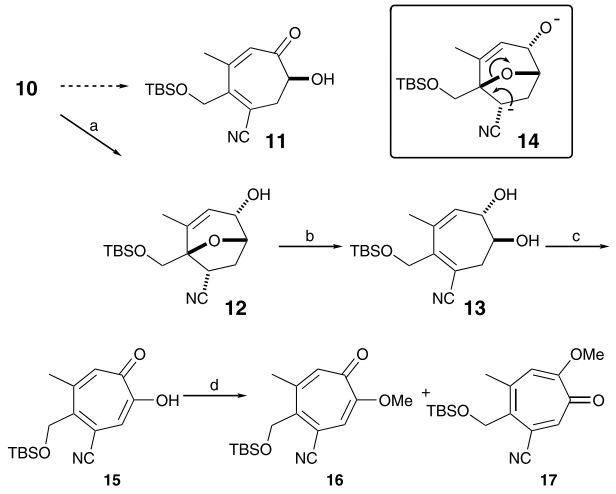
Scheme 2. General strategy for the synthesis of nitrile tropolones.

The 3-oxidopyrylium precursor **9**, which also served as a precursor to tropolone **1**, was thus derived in six steps from commercially available 3-methyl-2-furoate in excellent overall yield (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) $LiAlH_4$, THF, Et_2O, rt, 99%; (b) TBSCl, imidazole, DMF, rt, 90%; (c) *n*-BuLi, DMF, THF, –78°C to rt, 93%; (d) $NaBH_4$, EtOH/THF, rt, 1 h, 98%; (e) *m*-CPBA, DCM, –78°C, 3 h, 97%; (f) Ac_2O, DMAP, pyridine, 0°C, 90 min, 65%; (g) acrylonitrile (15 equiv.), toluene, 120°C, 6 h, 42%.

Heating pyranulose acetate **9** in toluene in the presence of acrylonitrile afforded cycloadduct **10** with complete regio- and *endo*-selectivity (as determined by NMR).[8] The moderate yield of this reaction is balanced by the high atom economy of this approach for the construction of the seven-membered ring system. With cycloadduct **10** in hand, the cleavage of the ether-bridge was investigated. In our previously disclosed tropolone synthesis, the ring cleavage of a related cycloadduct was achieved by an iodo-ether elimination that required several steps. For cycloadduct **10** we hoped to take advantage of the proximate nitrile group for the desired ether-bridge cleavage. Cycloadduct **10** was therefore treated with LDA (1–4 equiv.) in THF at –78°C and then warmed to ambient temperature, however no ring cleaved product **11** was isolated. In sharp contrast, allylic alcohol **12** underwent efficient ring cleavage.[9,10] Treating alcohol **12** with 2 equiv. of LDA in THF at –78°C and warming the reaction to ambient temperature afforded the desired ring-cleaved product **13** in good yield. The ability of **12** to undergo ring cleavage may be due to the instability of the di-anion **14** that is formed upon the addition of 2 equiv. of base. Finally, diol **13** was oxidised to the desired tropolone oxidation level in one step using the TFAA activated DMSO reagent followed by the addition of triethylamine and afforded tropolone **15** as a yellow solid in good purity (Scheme 4).



Scheme 4. *Reagents and conditions*: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 96%; (b) LDA (2 equiv.), THF, –78°C to rt, 68%; (c) DMSO (6 equiv.), TFAA (5 equiv.), –60°C, 1.5 h, then Et_3N (10 equiv.), 1.5 h; (d) CH_2N_2, THF, 2 h, 0°C, 70% over two steps.

Alternative oxidation procedures involving stepwise or slow oxidation procedures afforded none of the desired tropolone and led to intractable mixtures of products.[11] As with other tropolones synthesised within our laboratories, tropolone **15** could not be efficiently purified by silica gel chromatography. For full characterization and assignment, tropolone **15** was treated with diazomethane to afford the two expected regioisomers **16** and **17** as a 1:1 mixture in 70% yield.[12] Spectroscopic analysis showed that both tropolones featured the deshielded C–H resonances and IR stretches characteristic for the tropolone ring. The structures of isomers **16** and **17** were then fully assigned using 2D HSQC/HMBC NMR spectroscopy.

In conclusion, we have developed an efficient synthesis of novel highly substituted cyano-tropolones utilising a 3-oxidopyrylium [5+2] dipolar cycloaddition strategy. The incorporated nitrile substituent functions as an excellent handle for the cleavage of the ether-bridge. The cyano-tropolone is accessed in ten steps from a commercially available furan, which can be easily functionalized. The strategy and methodology developed thus opens the possibility of incorporating a large variety of substituents into the tropolone core.

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8. *Spectroscopic data for* ***10***: (colourless crystals) mp 84–85°C; IR ν_{max} (KBr)/cm^{-1} 2941m, 2239w, 1686s, 1465m, 1436w, 1248s, 1119s, 1003m, 907w, 834s, 777m; δ_H (400 MHz, $CDCl_3$) 0.10 (6H, s), 0.91 (9H, s), 2.04 (1H, ddd, J=13.5, 5.5, 1.5 Hz), 2.22 (3H, d, J=1.5 Hz), 2.82 (1H, ddd, J=13.5, 10.5, 8.5 Hz), 3.25 (1H, dd, J=5.5, 10.5 Hz), 3.96 (1H, d, J=11.5 Hz), 4.04 (1H, d, J=11.5 Hz), 4.59 (1H, apt. dt, J=8.5, 1.5 Hz), 6.03 (m, 1H); δ_C (100 MHz, $CDCl_3$) −5.57, −5.53, 18.17, 20.79, 25.67, 31.71, 32.47, 63.49, 80.96, 85.91, 118.40, 126.33, 162.17, 195.02; MS (CI, NH_4^+) 325 ([M+NH_4]$^+$, 100%), 308 ([M+H]$^+$, 55%) 250 (80%); MS (APCI+) 255 (-H_2C=CHCN); HRMS found 308.1693; $C_{16}H_{26}NO_3Si$ requires 308.1681.
9. A closely related cleavage of an oxy-bridge beta to a nitrile function in a [3.2.1] bicycle was previously reported. See: Marshall, K. A.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9135.
10. The stereochemistry of **12** was assigned using NOE NMR spectroscopy.
11. Oxidation procedures attempted include: MnO_2, IBX, PDC, PCC.
12. *Spectroscopic data for* ***16***: IR ν_{max} (KBr)/cm^{-1} 2930w, 2847w, 2218w, 1610s, 1592s, 1573s, 1462w, 1425w, 1388w, 1300m, 1245s, 1184m, 1129m, 1065s, 968w, 894w, 834s, 769m, 704w; δ_H (400 MHz, $CDCl_3$) 0.16 (6H, s), 0.92 (9H, s), 2.53 (3H, s), 3.96 (3H, s), 4.86 (2H, s), 6.61 (1H, s), 7.30 (1H, s); δ_C (125 MHz, $CDCl_3$) −4.89, 18.71, 25.31, 26.19, 57.09, 65.94, 111.30, 116.31, 119.66, 141.40, 146.43, 147.20, 163.41, 179.14; m/z (APCI+) 320 (MH$^+$, 50%); HRMS (CI+) found [MH]$^+$ 320.1675; $C_{17}H_{26}NO_3Si$ requires 320.1682.
Data for ***17***: IR ν_{max} (KBr)/cm^{-1} 2953m, 2851w, 2213w, 1616s, 1587m, 1469m, 1431w, 1399w, 1381w, 1293s, 1251s, 1186w, 1154w, 1122w, 1048s, 965m, 914w, 844s, 771s; δ_H (500 MHz, $CDCl_3$) 0.17 (6H, s), 0.93 (9H, s), 2.59 (3H, s), 3.98 (3H, s), 4.80 (2H, s), 6.73 (1H, s), 7.50 (1H, s); δ_C (125 MHz, $CDCl_3$) −6.22, 18.24, 25.67, 25.75, 56.35, 64.00, 118.35, 124.53, 134.58, 134.59 140.15, 145.65, 163.79, 172.12; m/z (APCI+) 320 (MH$^+$, 45%), 188 ([M−TBSO]$^+$, 100%); HRMS (CI+) found [MH]$^+$ 320.1671; $C_{17}H_{26}NO_3Si$ requires 320.1682.